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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/692,623	10/20/2000	Stephen M. Boyle	031786-046	2200

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GRASER, JENNIFER E	

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1645	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/692,623	Applicant(s) Boyle
	Examiner Jennifer Graser	Art Unit 1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *RCE and Amendt. C, 3/18/03*

2a)☐ This action is **FINAL.** 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24, 25, 27-30, and 35-43* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideratio

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24, 25, 27-30, and 35-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some* c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)

16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 16 & 27

18)☐ Interview Summary (PTO-413) Paper No(s). _____

19)☐ Notice of Informal Patent Application (PTO-152)

20)☐ Other:

DETAILED ACTION

Request for Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/18/03 has been entered.

Claims 24, 25, 27-30 and 35-43 are currently pending.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 24, 25, 27-30 and 35-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 24, 25, 27-30 and 35-43 are vague and indefinite because the methods recited in the independent claims are unclear. The methods include extracting DNA from a pathogenic microorganism, identifying at least one gene encoding at least one antigen from the DNA wherein said at least one antigen is capable of stimulating protective immunity against the pathogenic microorganism and inserting this at least one gene into a multicopy plasmid, inserting

the at least one gene into a multicopy plasmid capable of replicating and expressing in the pathogenic microorganism and transforming an attenuated or avirulent strain of the "otherwise pathogenic microorganism with the plasmid to form a vaccine...". This description is extremely vague and confusing. First, it is unclear what is meant by the recitation of an "otherwise" pathogenic bacteria because it is unclear what is encompassed by the phrase. Second, it is unclear whether the "pathogenic microorganism" and the "otherwise pathogenic microorganism" recited in all of the different parts are the same bacterium. The claim reads as if all of the DNA is being taken out of a cell and then just the gene encoding the desired antigen is being put back into the same cell. The claim does not make it clear that the microorganism in part (a) is different from the microorganism of parts (c) and (d). It appears that part (d) uses a different bacterium, i.e., an attenuated or avirulent strain, but the claim does not make this clear. The wording is extremely confusing. Figure 1 distinguishes between the bacterium used to find the desired gene and the bacterium which is transformed. Clarification and correction is required.

Claims 24, 27, 35 and 38 are vague and indefinite because the recitation "is capable of" merely describes the potential capability of the antigen to induce a protective or therapeutic immune response, but fails to positively recite that the antigen in fact induces such an immune response. The rejection can be obviated by changing the phrase "is capable of inducing" to --which induces--.

Claim 24 is vague and indefinite because it recites "a method for immunization, prophylaxis, or treatment of a vertebrate at risk or suffering from a disease caused by a

pathogenic microorganism". The pathogenic microorganism is said, in the last line of the claim, to be selected from the group consisting of *Brucella, Mycobacterium,* and *Vibrio.* It is unclear how a homologous antigen produced by a strain of *Brucella, Mycobacterium,* or *Vibrio* can induce protective or therapeutic immune response against any "pathogen". The term "pathogenic microorganism" encompasses fungi, viruses, parasites and bacteria from completely different species. Correction is required.

Claims 27 and 35 are vague and indefinite because they recite "a method for immunization, prophylaxis, or treatment of a vertebrate at risk or suffering from a disease caused by a *pathogenic* microorganism". The pathogenic microorganism is said, in the last line of the claim, to be selected from the group consisting of *Brucella.* It is unclear how a homologous antigen produced by a strain of *Brucella* can induce protective or therapeutic immune response against any "pathogen". The term "pathogenic microorganism" encompasses fungi, viruses, parasites and bacteria from completely different species. Correction is required.

Claim 38 is vague and indefinite because the wording is confusing. The last line of the claim recites that the "at least one gene" is a Cu/Zn SOD gene. If this is the case, then this should be inserted into part(b) of the claim where the "at least one gene" is recited. Further, the claim is vague and indefinite because it is unclear which microorganisms contain Cu/Zn SOD genes. Claim 40 recites *Brucella, Mycobacterium,*or *Vibrio.* However, it is unclear that *Vibrio* contains these genes. Claim 38 should be limited to bacteria that were known to contain these

genes at the time the invention was made provided there is support for these particular bacteria in the specification.

Additionally, claim 38 is vague and indefinite because it recites "a method for immunization, prophylaxis, or treatment of a vertebrate at risk or suffering from a disease caused by a *pathogenic* microorganism". .The last line of the claim recites that the "at least one gene" is a Cu/Zn SOD gene. It is unclear how a homologous antigen produced by a strain of bacteria that has the Cu/Zn SOD gene can induce protective or therapeutic immune response against any "pathogen", including those which do not naturally contain this gene. The term "pathogenic microorganism" encompasses fungi, viruses, parasites and bacteria from completely different species. Correction is required.

Claim 40 is vague and indefinite because the wording is confusing. The last line of the claim recites that the "at least one gene" is one or both of a GroES and a GroEL gene. If this is the case, then this should be inserted into part(b) of the claim where the "at least one gene" is recited. Further, the claim is vague and indefinite because it is unclear which microorganisms contain GroES and a GroEL genes. Claim 43 recites *Brucella, Mycobacterium,*or *Vibrio*. However, it is unclear that *Vibrio* contains these genes. Claim 40 should be limited to bacteria that were known to contain these genes at the time the invention was made provided there is support for these particular bacteria in the specification.

Additionally, claim 40 is vague and indefinite because it recites "a method for immunization, prophylaxis, or treatment of a vertebrate at risk or suffering from a disease caused

by a *pathogenic* microorganism". .The last line of the claim recites that the "at least one gene" is one or both of a GroES and a GroEL gene. It is unclear how a homologous antigen produced by a strain of bacteria that has the GroES and a GroEL gene can induce protective or therapeutic immune response against any "pathogen", including those which do not naturally contain these genes. The term "pathogenic microorganism" encompasses fungi, viruses, parasites and bacteria from completely different species. Correction is required.

Claims 25, 39 and 42 are vague and indefinite because of the phrase "said attenuated or avirulent version of the pathogenic microorganism further". This further clouds the issue as to whether of not all of the bacterium recited in the independent claims are the same. The phrase should be changed to --wherein said transformed attenuated or avirulent strain further---.

Claim Rejections - 35 USC § 112-Scope of Enablement

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 24, 25, 27-30 and 35-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "a method for immunization, prophylaxis or treatment of a vertebrate at risk or suffering from Brucellosis comprising inserting at least one of the genes for Cu/Zn SOD, GroES or GroEL into a multicopy plasmid and transforming an attenuated or avirulent strain of *Brucella* with the plasmid to form a vaccine and administering an effective amount of said vaccine to the vertebrate", does not reasonably provide enablement for "a method

for immunization, prophylaxis or treatment of a vertebrate at risk or suffering from a disease caused by *any* pathogenic microorganism (which includes viruses, fungi and parasites) comprising inserting at least one copy of *any* gene capable of stimulating a protective immune response against the pathogenic microorganism into a multicopy plasmid and transforming an attenuated or avirulent strain of the pathogenic microorganism with the plasmid to form a vaccine and administering an effective amount of said vaccine to the vertebrate", nor is the specification enabled for the broad scope of claim 38 which only limits the scope to at least one Cu/Zn SOD gene, but does not include which bacterium these genes come from or the pathogenic microorganism which is being treated, nor is it enabled form the scope of claim 41 which only limits the scope to at least one GroES or GroEL gene, but does not include which bacterium these genes come from or the pathogenic microorganism which is being treated. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant claims are broadly drawn to methods of providing prophylaxis, treatment or immunization of a vertebrate at risk of or suffering from *any* pathogenic microorganism comprising extracting DNA from the microorganism and performing research to discover a gene which encodes an antigen which is capable of stimulating a protective immune response against the pathogenic microorganism. The specification only provides results and written description for a method of treating Brucellosis by administering an attenuated strain of *Brucella* which has

been transformed with a multicopy plasmid comprising the gene for CU/Zn SOD antigen and/or the GroES or GroEL genes and does not enable the much broader scope of the claims. The recombinant vaccine art is highly unpredictable and even though the level of skill in the art is high, it would take undue experimentation for one to first locate a gene which when tested shows that it is capable of providing a protective immune response against disease in a pathogen. Challenge experiments are only provided for vaccines comprising *Brucella abortus* strain RB51 which over-expresses copper/zinc SOD and/or GroES/GroEL. The prior art teaches that most studies have shown that GroEL hsp proteins are ineffective as vaccines in preventing infections by various bacteria (see page 151 of Stevens et al. 1997. 20(2): 147-153. Comp. Immun. Microbiol. Infect Dis.). Stevens goes onto state that GroEL proteins from *Bordetella pertussis, Legionella pneumophila* and *Mycobacterium bovis* fail to induce significant protection from infection with these bacteria when mice or guinea pigs are vaccinated with these proteins. Accordingly, the claims broadly drawn to the use of attenuated strains containing a multicopy plasmid encoding a GroEL gene from strains other than *Brucella* are not enabled by the instant specification. Given the unpredictability with the GroEL antigen, there is insufficient evidence presented to enable one of skill in the art to select the appropriate genes and genuses of microorganisms out of the extremely large number of possibilities for application in the claimed method. Further, claims 41-42 do not recite which microorganisms the GroEL/ES genes are from, nor do they specify which microorganism they are treating. The claims blanketly suggest that any genes from 3 completely different Genus of bacteria can be used is not sufficient to

enable the invention. Other than a sweeping statement of other bacteria which may be used, the specification provides no concrete evidence of the protective ability or the structure of the genes from the vast number available to be used in the claimed methods.

The term "pathogenic microorganism" encompasses fungi, parasites, viruses and bacterium from completely different Genus. There is no description of fungi, parasites or viruses or their genes which encode protective antigens recited in the instant specification. This extremely broad scope is not enabled. Further, treating humans for tuberculosis is known in the art to be extremely difficult. There is no description of a recombinant attenuated strain carrying multicopies of a gene which encodes an antigen that would have the ability to provide protective immunity against this disease. It would take undue experimentation for one of skill in the art to accomplish this task. Further, no working examples are provided. Challenge experiments are necessary when prophylaxis or protective immunity is claimed. Additional evidences, in the form of Declaration, may be provided to enable a specific scope.

The specification also fails to teach any vaccines which would have the ability to protect against diseases caused by *Vibrio*. The specification fails to describe any genes which may be used to create these protective vaccines. Without such information, one of skill in the art could not predict which genes out of the vast numbers of genes which encode antigens would be able to provide a protective immune response in a vertebrate.

Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague

intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention."

In the instant case, a representative number of genes encoding protective antigens, which when transformed into an attenuated/avirulent strain of bacteria will provide immune protection in a vertebrate, as evidenced by challenge experiments, have not been disclosed. The concept of extracting DNA from an organism and searching for genes which may have potential to encode an antigen which may have potential to provide protective immunity is a vague intimation of a general idea that may or may not be workable. There is an inherent lack of predictability in the recombinant vaccine art in which one skilled in the art cannot readily anticipate the protective effects of any antigen or any transformed bacterial strain. Starting from the level of extracting DNA and then trying to identify protective antigens from the nucleic acid, which when asserted into a multicopy plasmid and transformed into a host is research and akin to discovering a new invention. Applicants are only entitled to methods for immunization, prophylaxis or treatment on vaccines that they have actually demonstrated to provide protection. They are not entitled to protection of yet to be discovered genes and yet to be discovered vaccines against diseases in

organisms they have not even contemplated. The scope of the claims should be limited to the evidences provided in the specification.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 24, 25, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kontinen et al (WO 94/19471) and Highlander et al. (US 6,180,112).

Kontinen et al disclose a method and expression system for enhancing secretion of hyperproduced homologous and heterologous exoproteins in bacteria. It is specifically taught that methods for overexpressing secreted proteins were readily available in the prior art, such as increasing gene expression by using multicopy plasmids or enhancing the activity of the gene by modifying its regulatory elements, e.g., by using strong promoters or multiple promoters, resulting in dramatic increases in the synthesis of exoproteins. See page 4, lines 15-20. It is also taught that this method and system may be used with any gram-positive bacterium (page 8, lines 7-8). It also may be used with any desired exoprotein, including any Gram-positive bacterium, antigenic proteins of microbes and protozoa and capsule, outer membrane and fimbria proteins from any Gram-negative bacteria, including ***M.tuberculosis, Vibrio cholerae***. It is also taught that any protein toxins or secreted proteins from bacteria, surface proteins of any microorganisms

and antigen proteins or viruses may be overexpressed in the same manner as taught in the reference. Accordingly, this would include *Brucella* as recited in instant claim 27. It is taught that these proteins may be used as vaccines and pharmaceuticals. See page 8, line 11-page 10, line 15. Additionally, the use of recombinant host cells which express an antigen that protects against disease, or the isolated antigen itself, were both widely used as vaccines in the prior art at the time the invention was made.

However, Kontinen et al. do not specifically disclose using the over-producing bacterial strains as vaccines, but rather teaches using the over-expressed products from the bacterial strains as the vaccines. Additionally, Kontinen et al. does not specifically recite the use of an attenuated or avirulent strain.

Highlander et al. discloses whole cell vaccine compositions comprising a recombinant, avirulent *Pasteurella haemolytica* organism which comprises a strong leukotoxin promoter which allows for homologous overexpression of said leukotoxin antigen. The *P.haemolytica* transcriptional activator is introduced on a multicopy plasmid (see bottom of column 42 and claim 8). It is specifically taught that since *P.haemolytica* leukotoxin genes are poorly expressed in *E.coli*, Pasteurella-specific transcriptional factors were used for this homologous, overexpression. Both methods and vaccine for the immunization, prophylaxis or treatment of vertebrates suffering from disease caused by *P.haemolytica* are specifically taught. The use of additional heterologous antigens are also taught. Highlander et al teach homologous over-

expression of a desired antigen in an attenuated strain of Gram-negative bacteria and the use of this strain as a vaccine.

The prior art teaches that the use of multicopy plasmids and/or using strong promoters or multiple promoters was well known in the bacterial art for increasing the production of a desirable protein product. The prior art also teaches that recombinant whole cell vaccines were well known. Kontinen et al teach that homologous over-expression was well known in the art. Highlander et al teach homologous over-expression of a desired antigen in an attenuated strain of Gram-negative bacteria and the use of this strain as a vaccine. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made that not only Gram-positive bacterium, but also attenuated or avirulent Gram-negative bacterium, as evidenced by Highlander et al., could be used to produce an homologous and/or homologous-heterologous expression system for the purpose of producing a vaccine. Highlander et al teaches that the expression system, itself, and not just the isolated expression products make effective vaccines. Further, official notice is taken that it was well known in the prior art that either the recombinant whole cell vaccine or the isolated product of a recombinant whole cell could be used as the major component in a vaccine composition.

The two references taken together provide motivation for using a whole cell vaccine with homologous over-expression. Kontinen teaches a method and expression system for enhancing secretion of hyperproduced homologous and heterologous exoproteins in bacteria. It is specifically taught that methods for overexpressing secreted proteins were readily available in the

prior art, such as increasing gene expression by using multicopy plasmids to overexpress a desired antigen or enhancing the activity of the gene by modifying its regulatory elements, e.g., by using strong promoters or multiple promoters (as done in Highlander et al.), resulting in dramatic increases in the synthesis of exoproteins. Highlander et al teach homologous over-expression of a desired antigen in an attenuated strain of Gram-negative bacteria and the use of this strain as a vaccine. Taken with Kontinen, it would have been obvious to one of ordinary skill in the art that the over-expression of leukotoxin taught by Highlander et al. could have also been achieved by the using multicopy plasmids to overexpress the desired protein instead of just using a multicopy plasmid comprising many copies of its activator. Kontinen teaches that both methods provide the same result, overexpression of a desired protein. It would have been obvious to one of ordinary skill in the art at the time the invention was made that not only Gram-positive bacterium, but also attenuated or avirulent Gram-negative bacterium, as evidenced by Highlander et al., could be used to produce an homologous and/or homologous-heterologous expression system for the purpose of producing a vaccine. Highlander et al teaches that the expression system, itself, and not just the isolated expression products make effective vaccines.

Response to Applicants' Arguments:

Applicants argue that the rejection is an "obvious-to-try" approach. They further aruge that this is insufficient to render obvious the selection of three particular genuses of bacteria out of an extremely large number of possibilities. This has been fully and carefully considered but is not deemed persuasive. Claims 24 and 27 are drawn to a broad generic method which is taught

by the prior art references. The instant claims provide no mention of the genes to be used or the pathogenic microorganism to be treated. The prior art references specifically teach that any antigenic proteins of microbes and protozoa and capsule, outer membrane and fimbria proteins from any Gram-negative bacteria, including ***M.tuberculosis, Vibrio cholerae*** may be used. It is noted that the concept of homologous over-expression was well known in the art at the time the invention was made, as demonstrated by the Highlander reference, as well as the Barzu reference submitted on Applicants PTO-1449. In response to applicant's arguments against the references **individually**, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Kontinen et al is almost so close to the claimed invention that it could almost be a 102(b). Although the reference does suggest the use of vaccines and pharmaceuticals, it does not particularly exemplify the use of the recombinant bacterium as the vaccine, but instead suggests the use of its over-expressed products. As stated above, Kontinen teaches a method and expression system for enhancing secretion of hyperproduced homologous and heterologous exoproteins in bacteria. It is specifically taught that methods for overexpressing secreted proteins were readily available in the prior art, such as increasing gene expression by using multicopy plasmids or enhancing the activity of the gene by modifying its regulatory elements, e.g., by using strong promoters or multiple promoters, resulting in dramatic increases in the synthesis of

exoproteins. See page 4, lines 15-20. It is taught that these products may be used as vaccines which by definition would confer protective immunity to a host.

Highlander et al. discloses whole cell vaccine compositions comprising a recombinant, avirulent *Pasteurella haemolytica* organism which comprises a strong leukotoxin promoter which allows for **homologous overexpression of said leukotoxin antigen**. The *P.haemolytica* transcriptional activator is introduced on a multicopy plasmid (see bottom of column 42 and claim 8). It is specifically taught that since *P.haemolytica* leukotoxin genes are poorly expressed in *E.coli*, Pasteurella-specific transcriptional factors were used for this homologous, overexpression. Both methods and vaccine for the immunization, prophylaxis or treatment of vertebrates suffering from disease caused by *P.haemolytica* are specifically taught. The prior art teaches that the use of multicopy plasmids and/or using strong promoters or multiple promoters was well known in the bacterial art for increasing the production of a desirable protein product. The prior art also teaches that recombinant whole cell vaccines were well known. Kontinen et al teach that **homologous over-expression** was well known in the art. Highlander et al teach **homologous over-expression of a desired antigen in an attenuated strain of Gram-negative bacteria and the use of this strain as a vaccine**. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made that not only Gram-positive bacterium, but also attenuated or avirulent Gram-negative bacterium, as evidenced by Highlander et al., could be used to produce an homologous and/or homologous-heterologous expression

system for the purpose of producing a vaccine. Highlander et al teaches that the expression system, itself, and not just the isolated expression products make effective vaccines.

8. Claims 24, 27, 28, 30, 35, 37, 41 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kontinen et al (WO 94/19471) and Highlander et al. (US 6,180,112) in further view of Stevens et al (Comp. Immun. Microbiol. Infect Dis.).

The teachings of Kontinen and Highlander et al are set forth above. However, they do not specifically teach the use of *Brucella abortus* strain RB51 or the overexpression of the GroEL heat shock protein.

Stevens et al disclose the vaccination of mice with attenuated *B.abortus* strain RB51 (abstract). Stevens also teach cloning the complete GroEL gene from Brucella into a regulatory high expression plasmid vector, pJE-7, to express the *B.abortus* GroEL protein at very high levels. The reference teaches that mice vaccinated with strain RB51 had significantly enhanced resistance when challenged with the wild-type strain and these mice displayed enhanced antibody responses to GroEL.

It would have been obvious to one of ordinary skill in the art at the time the invention was made that the a high expression vector or multicopy plasmid containing the GroEL gene could be transformed into the RB51 strain in order to enhance the immune response of the RB51 vaccine strain because Kontinen et al teaches a method and expression system for enhancing secretion of hyperproduced homologous and heterologous exoproteins in bacteria. It is specifically taught that methods for overexpressing secreted proteins were readily available in the prior art, such as

increasing gene expression by using multicopy plasmids or enhancing the activity of the gene by modifying its regulatory elements, e.g., by using strong promoters or multiple promoters, resulting in dramatic increases in the synthesis of exoproteins and Highlander et al teach homologous over-expression of a desired antigen in an attenuated strain of Gram-negative bacteria and the use of this strain as a vaccine. Taken with Kontinen and Highlander, it would have been obvious to one of ordinary skill in the art that the over-expression of GroEL taught by Stevens could have also been achieved by the using multicopy plasmids to overexpress the desired protein in the attenuated vaccine strain thereby increasing the immune response to the vaccine.

Note regarding Double patenting

4. The instant claims were restricted from the claims allowed in US Patent No. 6,149,920 during the prosecution of said parent application, formerly 09/091,521. The instant claims were also restricted from the claims pending in Divisional application 09/692,622 during the prosecution of parent application 09/091,521. Accordingly, a double patenting rejection cannot be made between the instant application and either of the related applications.

5. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is (703) 308-4242 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (703) 308-1742. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J Graser 4/16/03

JENNIFER E. GRASER
PRIMARY EXAMINER